Case Reports

Disseminated Coccidioidomycosis in a Patient With Acquired Immune Deficiency Syndrome

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THE ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) has been associated with alterations in cell-mediated immunity and with a variety of infections, including ones caused by fungi.[1] *Coccidioides immitis* infection occurs frequently in endemic areas, but usually causes asymptomatic or self-limited disease. Manifestations of disseminated disease occur in about 1% of those infected. At risk of disseminated disease developing are persons with underlying disorders of cell-mediated immunity, such as those suffering from reticuloendothelial malignancy and recipients of renal transplants. Pregnant women and members of certain ethnic groups including blacks and Filipinos are also at risk. Occasionally, disseminated coccidioidomycosis will develop in those without apparent risk factors.[2]

Alterations in cell-mediated immunity have been found in persons with disseminated disease due to *C immitis*. These include impaired cutaneous hypersensitivity responses to coccidioidin and dinitrochlorobenzene and depressed in vitro lymphocyte transformation and lymphokine production. These latter phenomena may result from increased T-cell suppressor activity.

Coccidioidomycosis has not previously been reported in patients with AIDS, but might be expected to disseminate in those infected because of the important role cell-mediated immunity plays in host defenses against coccidioidomycosis. We describe the case of a homosexual man with pulmonary coccidioidomycosis whose disease disseminated after AIDS had developed.

Report of a Case

A 30-year-old Hispanic homosexual man, a farm worker from the San Joaquin Valley, was admitted to Los Angeles County-University of Southern California Medical Center in January 1982 because of fevers to 40.5°C (104.9°F), night sweats, weight loss and hematochezia for three months. Three years before admission, a left upper lobe calcification on chest x-ray film, a positive coccidioidomycosis skin test and a coccidioidomycosis complement fixation (CF) titer of 1:2 had been noted. At that time, he was asymptomatic and received no treatment. He admitted to the occasional use of alcohol and amyl nitrate and to injecting drugs intravenously.

On admission he was cachectic and had a temperature of 38.9°C (102°F). He had posterior occipital lymphadenopathy and oral thrush. There were no chest findings, hepatosplenomegaly or skin rashes. The hemoglobin was 11 grams per dl and leukocyte count was 5,400 per μl with 71% segmented neutrophils, 5% band forms, 9% lymphocytes, 11% monocytes and 4% eosinophils. The erythrocyte sedimentation rate was 55 mm an hour. Liver function tests showed no abnormalities. Comparison of chest x-ray films from three years earlier showed new calcifications in both lower lobes, and cavitation of a previously noted upper lobe nodule. Computed tomography of the chest showed pronounced hilar adenopathy.

Purified protein derivative, coccidioidin (spherule-derived) spherulin (Berkeley Biol, Berkeley, Calif) and *Candida* skin tests were all negative. A sputum specimen contained budding cells. The cytomegalovirus CF titer was 1:8. The coccidioidomycosis CF titer was 1:32 and rose to 1:128 three months later. *Coccidioides immitis* was cultured from sputum, scalene node and urine specimens. A bone marrow biopsy specimen showed an early myeloproliferative syndrome. T-lymphocyte subsets were quantitated by direct immunofluorescence using commercial monoclonal antibodies (Ortho Diagnostic Systems Inc, Raritan, NJ): OK T_3 (T cells), 64%; OK T_4 (T-helper/inducer cells), 12%, and OK T_8 (T-suppressor/cytotoxic cells), 44%; B cells were 39%. The T helper-suppressor ratio was 0.3 (normal $\geq$1.0). Serum IgA level was 909 mg per dl (normal 150 to 400), IgG 1,630 mg per dl (normal 600 to 2,000) and IgM 314 mg per dl (normal 40 to 250).

The patient continued to have nightly temperature spikes to 40°C (104°F). On February 18 he was begun on a regimen of amphotericin B given intravenously, with gradual resolution of fever and symptoms. He received 1.3 grams of amphotericin at LAC-USC Medical Center and on April 22 he was transferred to a chronic care facility to complete a 1.4-gram course of amphotericin. On July 22 the patient was readmitted to LAC-USC Medical Center following one month of increasing weakness, anorexia, weight loss, problems

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immune deficiency syndrome
CF = complement fixation

in thinking, sore throat and dyspnea on exertion. Oral thrush was present. There was no lymphadenopathy or hepatosplenomegaly. The hemoglobin was 8.2 grams per dl, the platelets were normal in number and the leukocyte count was 2,900 per μl (80% segmented neutrophils, 1% band forms, 10% lymphocytes, 8% monocytes and 1% eosinophils). A lumbar puncture showed no abnormalities.

The patient had fevers each day to 39°C (102.2°F) and on the seventh hospital day hypoxemia and a left lung reticulonodular infiltrate developed. Methenamine silver stains of an open-lung biopsy specimen showed cysts of *Pneumocystis carinii*. Granulomas with *C immitis* spherules were also seen. His urine specimen again grew cytomegalovirus and *C immitis*. He was given trimethoprim-sulfamethoxazole and amphotericin B intravenously. Over the ensuing two weeks, however, his course was complicated by a persistent disseminated intravascular coagulopathy and respiratory failure. The patient died on August 17, 1982. At autopsy *C immitis* was found in cervical, mediastinal and peripancreatic lymph nodes. Granulomas with *C immitis*, cytomegalovirus inclusions in intraalveolar cells and *P carinii* were all present in lung tissue. A lymphoproliferative process thought to be an evolving immunoblastic sarcoma of B-cell type was found in the brain.

Discussion

AIDS is a recently recognized disorder of cell-mediated immunity in previously healthy persons that is manifested clinically by the occurrence of opportunistic infections and unusual tumors following a prodrome of fever, weight loss and fatigue.[3-5] The immunologic disorder is characterized primarily by T-cell dysfunction, as shown by anergy, lymphocytopenia and abnormalities found on in vitro T-cell studies, including reversal of the normal helper-to-suppressor T-lymphocyte ratio.[3-5] Although initially described in homosexual men and intravenous drug abusers, the population at risk is expanding and now includes Haitians and recipients of blood products.[6,7] As anticipated from the underlying immune defect, almost all infections in these patients are those in which the host depends primarily on cell-mediated immunity for defense. In addition to *P carinii*, infections due to *Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Toxoplasma*, cryptosporidia, cytomegalovirus, Epstein-Barr virus and *Herpesvirus hominis* (simplex) have been reported. *Candida* esophagitis and disseminated cryptococcosis are also frequent fungal infections.[1,3]

In North America, coccidioidomycosis is endemic to the western and southwestern United States and Mexico. Fungal infection is acquired by inhalation of arthrospores, thus establishing a primary focus in the lungs. Like tuberculosis, *C immitis* is believed to persist in tissues indefinitely and a host's immune defenses maintain microorganisms in latency.[2] An intact immune system with normally functioning macrophages, monocytes and lymphocytes is essential to a host's survival. Patients with primary uncomplicated coccidioidomycosis have positive skin tests, minimal changes on chest x-ray films and low CF titers. Immunosuppressed patients—especially those with cell-mediated immune abnormalities—are at an increased risk of reactivating primary foci or of fulminant disease developing during primary exposure. In particular, lymphocytopenia may predispose to dissemination.[8] Diagnosis is often made difficult by the fact that the predisposing or associated disease may mask the signs and symptoms of coccidioidomycosis. A negative skin test or a change from a previously positive test to a negative one, together with high or rising CF titers, is associated with severe disease and a poor prognosis.[2,8]

AIDS patients have pronounced T-lymphocyte abnormalities. Similarly, patients with progressive and disseminated coccidioidomycosis have been found to have both general and specific abnormalities of cell-mediated immunity. The numbers of T and B cells appear to be normal, but there is evidence of increased suppressor cell activity,[9] impaired production of macrophage migration-inhibiting factor and lymphocyte reactivity to specific antigens and mitogens.[10,11] Further, there seem to be disturbances in antigen recognition specific for *C immitis*.[10] These abnormalities have been found reversible in several patients who have recovered from disseminated disease.[9]

Because defense against coccidioidomycosis depends on cell-mediated immunity, persons with AIDS living in endemic areas may be expected to be at risk of disseminated disease developing. This case, however, is the first such report. The patient described clearly had AIDS and disseminated coccidioidomycosis, as indicated by high CF titers and recovery of *C immitis* from distant node sites and urine. His clinical and immunologic indices fit those previously described for AIDS. This patient also had a primary lymphoma of his central nervous system, now included in the Centers for Disease Control's case definition for AIDS.[12,13] Despite treatment with amphotericin B, resulting in the suppression of clinical symptoms and a stable CF titer to *C immitis*, the patient had persistent symptoms probably related to active infection, which parallels the experience of other AIDS patients in whom opportunistic infections tend to recur or persist following therapy.

Conclusions

The description of this case expands further the list of possible infectious agents occurring in AIDS and emphasizes the need for systematic evaluation in affected patients. Because the initial presenting symptoms of some AIDS patients may be only fever and adenopathy, coccidioidomycosis may never be considered. Such symptoms, in addition to pulmonary infiltrates,

skin lesions and even altered mental state, may be due to *C immitis,* a potentially treatable agent. Diagnosis should be aggressively pursued, both serologically and histologically, if the probability of a therapeutic response is to be maximized. All AIDS patients should be questioned about travel to endemic areas or any history of coccidioidomycosis, including skin testing. Lymph node involvement occurs frequently with coccidioidomycosis, as well; a lymph node biopsy should therefore be part of the work-up in patients suspected to have AIDS.[14,15] Because the most frequent sites of dissemination include skin, bone, meninges and the genitourinary system, appropriate cultures should be done. If there is any sign of dissemination, including reversals of a previously positive skin test or a rising titer, aggressive therapy with amphotericin B should be considered.

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Peritonsillar Abscess Associated With *Corynebacterium hemolyticum*

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Corynebacterium hemolyticum is a biochemically and clinically distinct species that has been increasingly recognized as a significant human pathogen. The first report of human infection by MacLean and co-workers[1] included more than 150 isolates, predominantly from the nasopharynx and skin. Subsequent reports[2-6] have confirmed the association with pharyngitis, often accompanied by a scarlatiniform rash, in young adults. In addition, there have been case reports of *C hemolyticum* isolated from brain abscesses,[7,8] blood,[9] osteomyelitis[10] and cutaneous abscesses, ulcers and paronychia.[1,4,5,10]

C hemolyticum involvement in the local suppurative complications of pharyngitis and tonsillitis has not been previously documented. We report three cases of peritonsillar abscess associated with *C hemolyticum.*

Reports of Cases

CASE 1. The patient, a 21-year-old college student, had been in good health with the exception of recurrent sore throats occurring several times per year. Approximately ten days before admission, a sore throat, predominantly on the left side, developed without associated symptoms. The soreness waxed and waned over the ensuing week until three days before admission when it increased greatly and odynophagia developed. Two days before admission he presented to the student health center where a Gram's stain from a tonsillar swab showed many leukocytes and mixed bacteria with a predominance of Gram-positive rods. Some hemolysis was noted on the culture, but the plate was too overgrown for specific identification to be made. His symptoms worsened and on a return visit to the health center penicillin VK, 500 mg four times a day, was prescribed. Over the subsequent 24 hours his condition continued to deteriorate and he was transferred to the hospital. On admission his symptoms included sore throat on the left side, dysphagia, odynophagia, trismus and voice changes. Physical examination revealed a bulging, swollen left tonsil and a temperature of 38°C (100.4°F). No rash was present. Results of initial laboratory studies were unremarkable except for a peripheral leukocyte count of 12,200 per cu mm with 78% neutrophils; no immature forms or atypical lymphocytes were noted. A Monospot test was negative.

He was placed on a regimen of intravenously given penicillin G, 1 million units every six hours, and was taken to the operating room the following morning after receiving three doses. Approximately 1 ml of pus was aspirated from the left peritonsillar area and a tonsillectomy carried out without complication. Gram's stain of the aspirate contained 4+ leukocytes and 3+ Gram-positive rods. The material was cultured both aerobically and anaerobically and yielded a pure growth of *C hemolyticum* sensitive to penicillin, ampicillin, tetracycline, erythromycin, clindamycin, vancomycin and cephalothin. Recovery was uneventful after intravenous administration of penicillin for one day fol-

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